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L6: Entry 1 of 2 File: USPT Jul 15, 2003

DOCUMENT-IDENTIFIER: US 6592623 B1
TITLE: Engineered muscle

Abstract Text (1):
A muscle implant includes an extracellular matrix, tendon and muscle cells. The extracellular matrix is made of a matrix of electrospun polymer fibers. The tendon is made of extruded collagen fibers and the muscle cells are disposed on the extracellular matrix in such a manner that the combination of components will functionally and structurally act as normal muscle tissue. Cardiac and smooth muscles may be similarly formed without tendons but including the extracellular matrix and muscle cells.

Brief Summary Text (11):
In one embodiment, a muscle implant includes an extracellular matrix made of electrospun fibers and muscle cells disposed on the matrix. In another embodiment, the muscle implant comprises an extracellular matrix made of electrospun fibers for supporting muscle, a tendon made of extruded fibers, and a muscle cell layer that is disposed on the extracellular matrix. The muscle cell layer can be multilayered. In other variations, the electrospun fibers may be cross linked. Also, an oriented layer of collagen can be deposited onto the extracellular matrix so that the muscle cells are disposed onto the oriented layer of collagen.

Brief Summary Text (12):
In another embodiment, the invention includes an extracellular matrix for supporting muscle comprising a matrix of electrospun fibers. The fiber is discharged from an electrically charged orifice onto a grounded substrate to form the matrix. The matrix can also be treated with cross linking agents so that the fibers are cross linked.

Brief Summary Text (13):
The invention also includes a method of manufacturing an extracellular matrix comprising extruding electrically charged polymer solution onto a grounded target substrate under conditions effective to deposit polymer fibers on the substrate to form an extracellular matrix. The extruded polymer may form a three-dimensional matrix. The extracellular matrix may further include a gel of aligned collagen fibers deposited thereon.

Drawing Description Text (2):
FIG. 1 is a scanning electron micrograph of an electrospun matrix of fibers.

Drawing Description Text (3):
FIGS. 2A and 2B are schematic drawings of electrospinning devices including the electrospinning equipment and a rotating wall bioreactor.

Detailed Description Text (5):
The engineered extracellular matrix of the present invention can be custom constructed to meet the requirements of skeletal, smooth or cardiac muscles. In preferred embodiments, the extracellular matrix is fabricated by electrospinning polymer fibers (synthetic or natural) to form a matrix directly onto a substrate; or to form a matrix directed onto a substrate or form (mold), or other surface such as the central cylinder of the RCCS Bioreactor (Synthecon).

Detailed Description Text (6):
There are a number of different kinds of bioreactors, devices designed to provide a low-shear, high nutrient perfusion environment, available on the market. Until recently, most of the available bioreactors maintained cells in suspension and delivered nutrients and oxygen by sparging, through the use of impellers, or other means of stirring. The RCCS bioreactor is a rotating wall bioreactor. It consists of a small inner cylinder, the substrate for the electrospinning process, positioned inside a larger outer cylinder. Although the electrospun matrix can be fabricated on the inner cylinder, other locations within the bioreactor also may be used for placement of the matrix for seeding. The gap between the inner and outer cylinders serves as the culture vessel space for cells. Culture medium is oxygenated via an external hydrophobic membrane. The low shear environment of the Synthecon RCCS bioreactor promotes cell-cell and cell-extracellular matrix (ECM) interactions without the damage or "washing away" of nutrients that occurs with active stirring or sparging. Typically, the RCCS device is operated at rotation rates of 8 up to 60 RPM, as required to maintain cells in suspension, and at less than 8 RPM (preferably 2-3 RPM) for cultures immobilized along the center shaft of the vessel. The Synthecon bioreactor can be used in a standard tissue culture incubator.

Detailed Description Text (7):
The electrospinning process can be used to produce a dense, mat-like matrix of unoriented polymer fibers (FIG. 1). "Electrospinning" means a process in which fibers are formed from a solution or melt by streaming an electrically charged polymer solution or melt through an orifice. Electrospinning has been used in the textile industry to produce ultra thin layers of fiber fabrics (continuous multi filaments) and dense mats of material. The polymer fibers formed by this technique are in the 40-500 nanometer diameter range. The mechanical properties (i.e., strength), porosity, and weight of the fabrics produced by electrospinning can be controlled by regulating the processing conditions, the materials used in the fabrication process and the thickness of the deposited material. Gibson, P. W., et al., Electrospun Fiber Mats: Transport Properties, 1998 AIChE J.; Deshi, J., et al., Electrospinning Process and Applications of Electrospun Fibers, 1996 J. Electrostatics 35:151.

Detailed Description Text (8):
An extracellular matrix of electrospun fibers in accordance with the present invention can be produced analogously. While any polymer can be used, it is preferable to electrospin natural polymer fibers such as collagen fibers. Various effective conditions can be used to electrospin a collagen matrix. While the following is a description of a preferred method, other protocols can be followed to achieve the same result. Referring to FIGS. 2A and 2B, in electrospinning collagen fibers, micropipettes 10 are filled with a solution of collagen and suspended above a grounded target 11, for instance, a metal ground screen placed inside the central cylinder of the RCCS bioreactor. A fine wire 12 is placed in the solution to charge the collagen solution in each pipette tip 13 to a high voltage. At a specific voltage determined for each solution and apparatus arrangement, the collagen solution suspended in the pipette tip is directed towards the grounded target. This stream 14 of collagen forms a continuous filament that, upon reaching the grounded target, collects and dries to form a three-dimensional, ultra thin, interconnected matrix of collagen (fabric). Minimal electrical current is involved in this process, and, therefore, the streaming process does not denature the collagen, because there is no expected temperature increase in the collagen solution during the procedure.

Detailed Description Text (10):
A variety of material can be supplemented into the electrospinning solution. DNA coding for desired products (vectors) can be mixed into the electrospinning polymeric solution for incorporation into the tissue-engineered scaffold. Upon consumption/reorganization of the scaffolding by the seeded cells, they may incorporate the vector (i.e. genetic engineering) into their DNA and produce a desired affect. The DNA can be in any form which is effective to enhance its uptake into cells. For example, it can be naked (e.g., U.S. Pat. Nos. 5,580,859; 5,910,488) or complexed or encapsulated (e.g., U.S. Pat. Nos. 5,908,777; 5,787,567). Similar to adding DNA, it may be possible to incorporate growth factors or other chemotaxins such as angiogenic factors into the electrospun matrix to aid in tissue regeneration.

Detailed Description Text (11):
The electrospinning process can be manipulated to meet the specific requirements for any given application. The micropipettes can be mounted on a frame that moves in the x, y and z planes with respect to the grounded substrate. In this way, the collagen or other polymer streamed from the micropipette can be specifically aimed or patterned. Although the micropipettes can be moved about manually, preferably, the frame onto which the micropipettes are mounted is controlled by a microprocessor and a motor that allows the pattern of streaming collagen to be predetermined by a person making a specific matrix. For instance, collagen fibers can be oriented in a specific direction, they can be layered, or they can be programmed to be completely random and unoriented.

Detailed Description Text (12):
In the electrospinning process, the polymer stream can branch out to form fibrils of the polymer. The degree of branching can be varied by many factors including, but not limited to, voltage, ground geometry, distance from micropipette tip to the substrate, diameter of micropipette tip, polymer concentration, etc. These variables are well-known to those of skill in the art of electrospinning microfiber textile fabrics.

Detailed Description Text (13):
The geometry of the grounded target can be modified to produce a desired matrix. In a preferred embodiment, a rotating wall bioreactor is used. The grounded target is a cylinder that fits inside the inner cylinder in the electrospinning process. By varying the ground geometry, for instance having a planar or linear or multiple points ground, the direction of the streaming collagen can be varied and customized to a particular application. For instance, a grounded target comprising a series of parallel lines can be used to orient electrospun collagen in a specific direction. The grounded target may be a cylindrical mandrel whereby a tubular matrix is formed. Most preferably, the ground is a variable surface that can be controlled by a microprocessor that dictates a specific ground geometry that is programmed into it. Alternatively, for instance, the ground may be mounted on a frame that moves in the x, y, and z planes with respect to a stationary micropipette tip streaming collagen. The grounded target 11 in FIG. 2B is shown as being able to oscillate along its longitudinal axis.

Detailed Description Text (16):
Other variations on electrospinning include: 1. Using different solutions (e.g.,. collagen I and III) to produce two or more different fibers simultaneously (matrix fiber array). In this case, the single component solutions can be maintained in separate reservoirs. 2. Using mixed solutions (e.g., collagen I and III) in the same reservoir(s) to produce fibers composed of multiple polymers (fiber composition "blends"). Nonbiological but biologically compatible material can be mixed with a biological molecule such as collagen, e.g., PVA, PLA, PGA, PEO, etc. 3. Utilizing multiple potentials applied for the different solutions or even the same solutions. 4. Having two or more different geometric grounded targets (i.e. small and large mesh screens).

Detailed Description Text (18):
The stability, rigidity, and other attributes of the electrospun matrix can be regulated by the degree to which it is chemically modified. The electrospun matrix may be used in its unmodified state, or it may be modified in accordance with the requirements of a specific application. Modifications to the matrix can be made during the electrospinning process or after it is deposited. Cross-linking agents such as carbodiimide EDC (1-ethyl-3(3 dimethyl aminopropyl)), carbodiimide hydrochloride, NHS (n-hydroxysuccinimide), or UV light can be used e.g., to stabilize the fascial sheath against proteolytic attack, and/or to increase the stability of collagen gels. See, e.g., Van Wachem, et al., 1996 Myoblast seeding in a collagen matrix evaluated in vitro, J. Biomedical Materials Res. 30:353-60.

Detailed Description Text (20):
The engineered tendon, or the connective tissue struts that anchor the engineered muscle to bone, can be assembled from extruded collagen fibers or other suitable materials. Collagen fibers are preferred, because collagen is less likely to be

rejected by a recipient's immune system. These fibers function in combination with the extracelluar matrix to stabilize the overall structural integrity of the muscle implants. Collagen fibers for the fabrication of the engineered tendon can be extruded after known methods. Kato, Y. P. and Silver, F. H., Formation of Continuous Collagen Fibers: Evaluation of Biocompatibility and Mechanical Properties, 1990 Biomaterials 11: 169-75; Kato, Y. P., et al., Mechanical Properties of Collagen Fibers: A Comparison of Reconstituted Rat Tendon Fibers, 1989 Biomaterials 10:38-42; and U.S. Pat. Nos. 5,378,469 and 5,256,418 to Kemp, et al.

Detailed Description Text (21):
A preferred collagen extrusion apparatus comprises a syringe pump, microbore tubing, a dehydration trough, recirculation pump, rinsing trough, drying chamber, heating air dryer, and a collagen fiber winder. The syringe is filled with degassed collagen and mounted onto a syringe pump. The collagen solution is then extruded from the syringe, through the microbore tubing, and into a dehydration bath (Polyethylene glycol in PBS). The formed collagen fiber is subsequently guided through a rinsing bath (phosphate buffered saline, PBS) and attached to a winding system within a dryer. Once the initial fiber has been formed and attached to the winding element, the process becomes automated and continuous. At an extrusion rate of approximately 8 cm/minute, the extrusion apparatus can produce fiber 1-10 meters in length and 50-250 .mu.m in diameter. After production, the fiber diameter can be verified through scanning electron and light microscopic evaluation. Varying the reaction conditions controls the diameter of the collagen fiber that is polymerized. The physical properties of the engineered collagen fiber can be further modified and controlled by regulating the composition of the extrusion material. The elastic properties of the engineered tendon can be modulated by incorporated elastin, fibrin or man made material into the collagen solution as it is extruded. Prior to use in the engineered implant the collagen fibers are sterilized by peracetic acid sterilization.

Detailed Description Text (29):
The muscle implant can comprise three distinct components, the extracellular matrix, the engineered tendon and the population of muscle cells. As detailed earlier, an extracellular matrix composed of a matrix of collagen fibers or other biologically compatible material is prepared on the outer surface of the inner cylinder of an RCCS bioreactor (or suitable substitute). The structural properties of this mat of fibers are regulated by the diameter of fibers produced, the relative concentration of materials used in the reaction (e.g. concentration of type I to type III collagen, or other incorporated materials), and other reaction conditions.

Detailed Description Text (30):
In one preferred embodiment, a thin gel matrix of collagen or other suitable matrix material can be applied over the surface of the extracellular matrix to enhance muscle cell adhesion, differentiation, and/or alignment. The gel matrix can be applied in any suitable manner including electrospinning, spraying, dipping, spreading, dropping, etc. Simpson, et al., Modulation of Cardiac Phenotype in vitro by the Composition and Organization of the Extracellular matrix, 1994 J. Cell Physiol. 161:89-105. In a preferred embodiment, the collagen fibers in the thin gel are aligned along a common axis. For example, the aligned matrix can be produced by dipping the central cylinder core of the RCCS bioreactor, with its electrospun coating of collagen, end-on into a ice cold neutral stock solution of collagen (1 mg/ml) (Type I or type III or a mixture thereof). After a very brief interval (1-3 secs), the cylinder is removed from the solution and the excess collagen is allowed to drain by gravity off of the distal end of the cylinder. The orientation of the cylinder is maintained constant throughout this process, i.e. perpendicular to the collagen solution in which it was dipped. This allows the excess collagen to drain off the long axis of the cylinder. The cylinder is then placed into an incubator, e.g., set for 37.degree. C, to allow the collagen to polymerize, e.g., sixty minutes or more. After polymerization is complete, the aligned collagen fibers are allowed to dry down on to the underlying facial sheath. These procedures result in a thin layer of aligned collagen fibrils arrayed along the axis the cylinder was drained. See FIG. 3. Other methods for aligning the collagen may be employed, for instance, using the described electrospinning system or using a centrifuge after dipping the core in the collagen solution. Regardless of how the collagen is aligned, at the conclusion of this step, the central RCCS cylinder has a mat-like coating of

electrospun collagen fibers (the extracellular matrix) covered or coated with a thin layer of aligned collagen.

Detailed Description Text (32):
Also, as discussed earlier, the need for the thin gel of collagen fibers may be obviated if the electrospun matrix is sufficiently oriented during the electrospinning process. In other words, the additional thin gel layer of oriented collagen is only necessary if the extracellular matrix (fascial sheath in the example of skeletal muscle) of collagen or other polymer is unoriented.

Detailed Description Text (33):
Large diameter, extruded collagen fibers (engineered tendons) are then applied over the aligned collagen gel. The mechanical properties of the implant are controlled in this step at two separate sites. First, by the thickness of the individual extruded fibers and the number of these filaments added to the implant. Second, by the orientation of these fibers with respect to the long axis of prosthesis. The implant can be made more or less stiff by applying these fibers in an undulating pattern. The large fibers can also be attached to the matrix by only overlapping the matrix at the distal ends, i.e., not necessarily running the entire length of the engineered muscle. Regardless of the orientation used, the ends of extruded fibers are allowed to project from the distal ends of the implant. At the conclusion of this step, the large diameter collagen fibers are allowed to dry down onto the fibers of the aligned collagen gel. Alternative fabrication processes can be used to further customize the mechanical properties of the implant. For example, large diameter collagen fibers may be laid down first followed by collagen fibers deposited by electrospinning, followed by another layer of large diameter collagen fibers, the aligned collagen gel and the satellite cells. Other permutations on this assembly process are also possible.

Detailed Description Text (35):
In the final step of the fabrication process, the inner cylinder with its engineered fascial sheath and overlaying layers of aligned collagen and large diameter collagen fibers is loaded into a RCCS bioreactor. Muscle cells, such as satellite myoblasts isolated from the subject or compatible donor, are loaded into the chamber and allowed to interact with the collagen-based substrate. The RCCS bioreactor is preferably used in this step because it provides high nutrient profusion in a very low shear environment. However, other culture vessels can be used. Under these conditions, it is possible to assemble a muscle cell culture comprising multiple layers (8-12layers in 48 hours) of aligned cells. In the assembly of the muscle implant, cells are gradually depleted from suspension culture and plated onto the collagen matrix, either directly on the electrospun matrix or on the collagen gel coating, to form the three dimensional arrangement of the engineered tissue. Additional satellite cells are added as need to the bioreactor to assemble additional cell layers. Once the desired mass of cells has been plated onto the fascial sheath, they are allowed to differentiate into myotubes, e.g., by transfer to a serum media. Also, there are artificial oxygen carriers that can be used in vitro to increase oxygen delivery to tissues or cells in culture. They would be mixed into the reactor with the satellite cells as the muscle is fabricated. They basically function like red blood cells.

Detailed Description Text (37):
With the completion of the differentiation process, the skeletal muscle implant is ready for transplantation into the site of reconstruction in the subject. The implant is removed from the central cylinder of the bioreactor. The size and thickness of the implant is controlled at this stage of the process at two different levels--first, by the number of cell layers assembled onto the central cylinder and, second, by the size of the sheet of tissue used to construct the muscle implant. This latter procedure involves trimming (for instance, into a rectangular sheet--FIG. 5A), stacking, and rolling (FIG. 5B) the engineered muscle into the desired configuration. Alternatively, the engineered muscle can be directly implanted or layered for the reconstruction of, for instance, facial muscles as a flat sheet. If the engineered muscle is to be used to reconstruct a muscle bed of the axial skeleton, it may be attached to the implantation site through the large diameter collagen fibers 20 that protrude from the ends of engineered muscle 21, through the distal ends of the fascial sheath itself or through a combination of

these methods.

Detailed Description Text (38):
If the tissue is to be used to reconstruct a congenital heart defect or repair an otherwise dysfunctional region of myocardium or reconstruct a muscle of facial expression it can be sutured or affixed in place with fibrin glue. By modifying the assembly process, implants for the reconstruction of cardiac muscle or smooth muscle can be assembled. In general, the major modification may be in the relative pattern of the engineered extracellular matrix and connective struts or tendons described in this application. Cardiac tissue and smooth muscle lack tendons. However, the use of large diameter collagen fiber may still be desirable to lend mechanical strength to the implant. In the case of cardiac implants, the large fibers may be used as a delivery system to assemble the implants. The key common feature to assembly of these implants is the ability to fabricate a multi-layer implant composed of cells in an in vivo pattern of organization.

Detailed Description Text (40):
The engineered muscle described above is advantageous in several respects. First, the connective backbone support of the implant comprises natural materials. This material has low antigenic potential and its structural properties can be regulated at many different sites, including, but not limited to; the relative concentration of different collagen isoforms used to produce the sheath, the thickness of the fibers used and, the degree of chemical cross-linking present in the matrix. Next, the implant uses large diameter collagen fibers to further modify the structural properties of the implant and provide a means to anchor the engineered muscle to the site of transplantation. These fibers are very similar to the fibers used to manufacture catgut for surgical sutures (>250 .mu.m), however, the extrusion process allows for better control of fiber diameter and the fabrication of fibers that are much smaller in diameter than conventional catgut (50 to 200 .mu.m depending upon reaction condition). Preliminary studies from other laboratories indicate the efficacy of using extruded collagen fibers in the production of tendons in the rat and in the formation of woven sheets for the repairs of experimental abdominal wounds in the rat. The implantation of large diameter, extruded collagen fibers did not induce inflammation beyond background levels in these experiments.

Detailed Description Text (44):
In vivo deneravation of skeletal muscle promotes the evolution of atrophy in the effected tissue. To a great extent, this response appears to develop because deneravation reduces the amount of resting tension observed in the affected muscle (Thomsen and Luco 1944; Gutman et al., 1971). In vitro, the effects of denervation may be substantially overcome by applying tension to the denervated muscle. Cardiac muscle is also very sensitive to its surrounding medical environment. Muscle mass may be initially retained in an engineered prosthesis by placing it under tension at the time it is implanted. Different methods of hypertrophy or stretching of the implant are available. A mechanical stretcher can be used in the bioreactor by attachment of the "tendons" on either end of the implant to ring clamps to tighten or loosen the implant. FIG. 6 illustrates how the fibers will be held in place (at desired orientations longitudinally) on the inner cylinder surface of the bioreactor by two end supports 30. FIG. 6 also illustrates the use of motor driven screw 31 drives to be added to the bioreactor to allow mechanical stretching (well defined percentage of stretch) for preconditioning particular tissue (muscle, blood vessels, and intestines) during the initial cell seeding/development stage. The stretching makes bigger, thicker and stronger cells/tissue that are less likely to tear after implantation. The stretching can also be used to further align the muscle cells. Electrical pacing or pharmacological stimulation can also be used. Electrical pacing, in particular, is very effective and easy to control.

Detailed Description Text (46):
Example 1 Electrospinning an Extracellular Matrix

Detailed Description Text (47):
An extracellular matrix was made of poly-lactic/poly-glycolyic acid (PLA/PGA; 50/50--RESOMER.RTM. RG 503, Boehringer Ingelheim, Germany) and poly(ethylene-co-vinyl) acetate (Aldrich Chemical Company, Inc., Milwaukee, Wis.) polymers. The concentration of the two polymers dissolved in dichloromethane

(Sigma-Aldrich, St. Louis, Mo.) were 0.19 g/ml RESOMER.RTM. RG 503 and 0.077 g/ml poly(ethylene-co-vinyl) acetate. The electrospinning set-up consists of a glass pipet (overall length approximately 21 cm with a tapered tip with an opening estimated at 0.3 mm, no exact measurement obtained, 0.32 mm diameter silver-coated copper wire, 20.times.20 mesh 316 stainless steel screen, two large clamp holders (polymeric coated), base support, and a Spellman CZE1000R power supply (0-30,000 volts, Spellman High Voltage Electronic Corp., Hauppauge, N.Y.). The physical set-up had the top clamp holder containing the glass pipet at approximately 12 inches from the base with the pipet tip pointing (pipet at approximately at 45 angle to base) toward the base. The wire was then placed in the top of the glass pipet and inserted until reaching the pipet tip where it remained during the procedure. The second clamp holder was placed at approximately 6 inches above the base for holding the screen (grounded target) approximately perpendicular to the axis of the glass pipet. The distance between the pipet tip and the grounded screen was approximately 10 cm. The positive lead from the high voltage power supply was attached to the wire hanging out the top end of the glass pipet while the negative lead (ground) was attached directly to the stainless steel screen. The glass pipet was then filled with the appropriate solution and the power supply turn on and adjusted until electrospinning was initiated (i.e. fibers shooting from the tip of the glass pipet). This stream (splay) of solution begins as a monofilament which between the pipet tip and the grounded target is converted to multifilaments (electric field driven phenomena). This allows for the production of a "web-like" structure to accumulate at the target site. Upon reaching the grounded target, the multifilaments collect and dry to form the 3-D interconnected polymeric matrix (fabric). The apparatus described is conceptually the same as the set-up illustrated in FIGS. 2A and 2B. All described studies and solutions are at room temperature. The fibers produced by these preliminary studies ranged from 1-100 microns in diameter with both polymeric solutions evaluated. The thickness of the matrices produced was not measured. Although, the thickness of the matrix that can be produced is dependent on the amount of polymer solution (spinning time) utilized and allowed to accumulate in a particular region. Thus, allowing the ability to produce a matrix with varying thickness across the sample. A scanning electron micrograph of the fiber forming the matrix is shown in FIG. 1.

Other Reference Publication (2):
Electrospun Fiber Mats: Transport Properties, Gibson et al., Accepted AICHE, Oct. 98.

Other Reference Publication (3):
Electrospinning Polymer Fibers, Schreuder-Gibson, SSCNC-YM, U.S. Army Natick Research, Development and Engineering Center, 1997.

Other Reference Publication (15):
Nanometre Diameter Fibres Of Polymer, Produced By Electrospinning, Reneker et al., Nanotechnology 7, pp. 216-223, 1996.

Other Reference Publication (17):
Mechanical Properties of Collagen Fibres: A Comparison Of Reconstituted And Rat Tail Tendon Fibres, Kato et al., Biomaterials, vol. 10, Jan. 1989.

Other Reference Publication (18):
Formation Of Continuous Collagen Fibres: Evaluation Of Biocompatibility And Mechanical Properties, Kato et al., Biomaterials, vol. 11, Apr. 1990.

Other Reference Publication (40):
Effects of Static Axial Strain on the Tensile Properties and Failure Mechanisms of Self-Assembled Collagen Fibers, Pins et al., University of Medicine and Denistry of New Jersey, Robert Wood Johnson Medical School, pp. 1429-1440, Dec. 22, 1997.

Other Reference Publication (41):
Self-Assembly of Collagen Fibers, Influence of Fibrillar Alignment and Decorin on Mechanical Properties, Pins et al., Biophysical Journal, vol. 73, pp. 2164-2172, Oct. 1997.

Other Reference Publication (45):

Electrospinning Process and Applications of Electrospun Fibers, Doshi et al., Journal of Electrostatics, 35, pp. 151-160, 1995.

Other Reference Publication (77):
Electrospinning Process and Applications of Electrospun Fibers, Doshi et al., Journal of Electrostatics, 35 (1995) 151-160.

CLAIMS:

1. A muscle implant comprising: an extracellular matrix for supporting muscle, a tendon comprising extruded fibers, a muscle cell layer, and an oriented layer of collagen deposited onto the extracellular matrix wherein the muscle cells are disposed onto the oriented layer of collagen.

9. The method described in claim 6, wherein the tendon is formed by extruding collagen fibers.

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L6: Entry 1 of 2 File: USPT Jul 15, 2003

US-PAT-NO: 6592623
DOCUMENT-IDENTIFIER: US 6592623 B1

TITLE: Engineered muscle

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US-CL-CURRENT: 623/14.13; 623/13.17

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 6265333 B1

L6: Entry 2 of 2 File: USPT Jul 24, 2001

US-PAT-NO: 6265333
DOCUMENT-IDENTIFIER: US 6265333 B1

TITLE: Delamination resistant composites prepared by small diameter fiber reinforcement at ply interfaces

DATE-ISSUED: July 24, 2001

INVENTOR-INFORMATION:

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US-CL-CURRENT: 442/346; 156/276, 428/300.7, 428/903, 442/381, 442/392

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